Complete Summary

GUIDELINE TITLE

ACR Appropriateness Criteria® rectal cancer - metastatic disease at presentation.

BIBLIOGRAPHIC SOURCE(S)

Herman J, Messersmith WA, Johnstone PA, Blackstock AW, Konski AA, Mohiuddin M, Poggi MM, Regine WF, Rich TA, Suh WW, Cosman BC, Saltz L, Expert Panel on Radiation Oncology--Rectal/Anal Cancer. ACR Appropriateness Criteria® rectal cancer--metastatic disease at presentation. [online publication]. Reston (VA): American College of Radiology (ACR); 2007. 6 p. [27 references]

GUIDELINE STATUS

This is the current release of the guideline.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
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SCOPE

DISEASE/CONDITION(S)

Rectal cancer with metastatic disease

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Colon and Rectal Surgery
Family Practice
Gastroenterology
Internal Medicine
Oncology
Radiation Oncology
Radiology
Surgery

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of therapeutic procedures for rectal cancer with metastatic disease

TARGET POPULATION

Patients with rectal cancer and metastatic disease at presentation

INTERVENTIONS AND PRACTICES CONSIDERED

Management/Treatment

1. Surgery
    - Resection of rectal primary tumor and liver lesions (concurrent or sequential)
    - Resection of liver lesion only
    - Surgical debulking of metastatic disease
    - Resection of rectal primary tumor
2. Chemotherapy
    - FOLFOX (oxaliplatin, 5-fluorouracil, and folinic acid) or FOLFIRI (leucovorin, 5-fluorouracil, and irinotecan) with or without bevacizumab
3. Radiotherapy: Pelvic radiotherapy alone
4. Combination therapy: preoperative pelvic radiotherapy with concurrent 5-fluorouracil-based chemotherapy
5. Liver-directed therapies (transarterial embolization, radiation, radiofrequency ablation)
6. Stent or loop colostomy to relieve obstruction
7. Best supportive care

MAJOR OUTCOMES CONSIDERED

- Progression-free survival rate
- Overall survival rate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi

technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table and narrative as developed by the topic leader(s). Questionnaires are completed by participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Rectal Cancer—Metastatic Disease at Presentation

Variant 1: Initial treatment for a 52-year-old male without a significant past medical history and an asymptomatic nonobstructing rectal uT3N0 primary metastasis 8 cm from the anal canal and a solitary 4 cm metastasis in right lobe of the liver. KPS 90.

Treatment	Rating	Comments
Initial resection of rectal primary and liver lesion (either concurrent or sequential)	8	
Initial systemic 5FU-based chemotherapy (FOLFOX/FOLFIRI +/- bevacizumab)	5	
Initial preoperative pelvic RT + concurrent 5FU-based chemotherapy	3	
Resection of the liver lesion only	2	
Best supportive care	1	
Rating Scale: 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: Initial treatment of a 60-year-old female without a significant past medical history, and an asymptomatic non-obstructing uT3N0 rectal cancer, bilobar hepatic metastases (50% liver replacement) and bilateral pulmonary metastases. KPS 90.

Treatment	Rating	Comments
Systemic 5FU-based chemotherapy(FOLFOX/FOLFIRI +/- bevacizumab)	9	
Best supportive care	2	
Surgical debulking of metastatic disease	1	
Resection of rectal primary	1	
Liver directed therapies (transarterial embolization, radiation, RFA)	1	
Preoperative pelvic RT + concurrent 5FU-based chemotherapy	1	

Treatment	Rating	Comments
Rating Scale: 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: Initial treatment of a 60-year-old female without significant past medical history, with uT3N0 rectal cancer, bilobar hepatic metastases (50% liver replacement) and bilateral pulmonary metastases. Rectal lesion causing pain and early symptoms of obstruction. KPS 80.

Treatment	Rating	Comments
Initial preoperative pelvic RT + concurrent 5-FU based chemotherapy	7	
Initial systemic 5FU-based chemotherapy (FOLFOX/FOLFIRI)	6	
Initial palliative stent or loop colostomy to relieve obstruction	5	
Initial systemic 5FU-based chemotherapy (FOLFOX/FOLFIRI + bevacizumab)	4	
Initial resection of rectal primary	3	
Initial pelvic RT alone	2	
Initial surgical debulking of metastatic disease	1	
Initial liver directed therapies (transarterial embolization, radiation, RFA)	1	
Best supportive care	1	
If Preoperative RT + Chemo Given: RT Dose		
45 Gy/1.8 Gy	5	
50.4 Gy/1.8 Gy	8	

Treatment	Rating	Comments
54 Gy/1.8 Gy	7	
59.4 Gy/1.8 Gy	3	
Rating Scale: 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: Initial treatment of a 74-year-old female with history of coronary artery disease, severe emphysema, diabetes, now with an asymptomatic nonobstructing uT3N0 rectal primary with extensive hepatic metastases and abdominal carcinomatosis. Poor oral intake. KPS 50.

Treatment	Rating	Comments
Best supportive care	8	
Systemic chemotherapy	2	
Resection of rectal primary	1	
Preoperative pelvic RT + concurrent 5FU-based chemotherapy	1	
Resection of metastatic disease	1	
Rating Scale: 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

In 2007, an estimated 41,420 new cases of rectal cancer will be diagnosed in the United States (23,840 men and 17,580 women). After decades of treating metastatic colorectal cancer (CRC) with 5-fluorouracil alone, newer agents have resulted in significant improvements in disease-free and overall survival rates. These improvements stem from combinations of newer cytotoxic agents (irinotecan and oxaliplatin) and targeted therapies (cetuximab and bevacizumab). Based on performance status and the burden of disease (resectable liver-only or lung-only vs. widely systemic disease), metastatic CRC patients are generally treated with either curative or palliative intent.

Management of patients with newly diagnosed metastatic rectal cancer may be complicated, and will benefit in most cases from multidisciplinary specialty input

pretreatment. Treatment decisions must be individualized based on the overall medical condition of the patient, the extent and distribution of extrapelvic metastatic disease, and the patient's wishes. As this is an uncommon presentation of rectal cancer, specific literature on the subject is sparse, and conclusions must be drawn from extrapolation of management principles for metastatic colon cancer.

Management of Patients with Colorectal Liver Metastases

Patients with resectable colorectal liver metastases and no evidence of any extrahepatic metastases have impressive 5-year survival rates of 30% to 70% following resection. Unfortunately, only 20% to 30% of patients with colorectal liver metastases are candidates for resection at initial presentation. Management should be based on whether the patient has resectable disease and is an appropriate candidate for antitumor treatment, or whether debilitation has progressed to the degree that supportive care is more appropriate. In general, patients with minimal comorbidities and a Karnofsky performance status (KPS) of 80% to 100% should be managed aggressively. Otherwise, these patients may be more appropriate for less aggressive treatment, and in some extreme cases, they may be best served by supportive and/or comfort-oriented care only.

In a patient deemed fit for aggressive intervention, a determination must be made as to whether the patient is potentially treatable for cure, or whether treatment is strictly palliative. Potentially curable patients, for all practical purposes, are those with metastatic disease that is confined to a single organ (usually liver or lung) in a distribution permitting complete resection. Patients with metastases in multiple organs can sometimes receive aggressive local and systemic therapies if fit for treatment and have limited extrahepatic tumor burden. Whether patients with multiple liver lesions can undergo a curative resection is based on the number, size, and location of the lesions. Otherwise patients with unresectable disease are approached with palliative local or systemic therapy and/or supportive care.

Curative Surgical Intent in Patients with Colorectal Liver Metastases

In a patient treated with curative intent, the potential for such curability is confirmed by noninvasive imaging and/or surgical exploration to exclude unsuspected metastases to intra-abdominal organs, lymph nodes, and peritoneal surfaces. If the primary rectal tumor and metastatic disease are resectable and the primary lesion is nonobstructing, patients may undergo a staged resection in which the liver tumor is resected first. If this is accomplished successfully, then resection of the primary is undertaken. A single (synchronous) procedure can be performed if a metastatic liver lesion can be removed through the same midline procedure as the lower anterior resection without compromising the quality of the liver resection. Patients undergoing abdominal-perineal resection and/or patients requiring a subcostal or other additional incision for resection of the metastases should usually undergo staged procedures.

Adjuvant/Neoadjuvant Chemotherapy for Liver Metastases

There is a clear survival benefit from resection in patients with limited hepatic metastases from CRC; however, the role of systemic or regional therapy following resection of metastases is less clear. Perioperative FOLFOX (oxaliplatin, 5-

fluorouracil, and folinic acid) for three months prior to and after resection of liver metastases appears safe, and an advantage in 3-year disease-free survival rates has been demonstrated. Patients with solitary or a small number of lung metastases may also benefit from aggressive resection, but data are limited.

Currently, only retrospective data support the use of neoadjuvant chemotherapy and/or liver-directed therapies to increase the likelihood of resecting initially unresectable liver-limited metastasis. The advantages of potential downstaging with neoadjuvant chemotherapy must be weighted against potential adverse effects such as steatohepatitis and vascular changes, which may increase surgical complications.

Unresectable Liver Metastases

The primary management of unresectable metastatic disease is systemic chemotherapy. Some uncontrolled trials have investigated liver-directed therapies such as transarterial embolization (TACE), chemoradiation, radiofrequency ablation, and cryotherapy in the palliative or, in rare cases, neoadjuvant setting in colorectal cancer. Randomized studies with long-term follow-up are needed to determine the efficacy of these modalities.

Management of the Primary in Patients with Resectable Metastatic Disease

The optimal management of this patient population is controversial; however, the paradigm is changing with the substantial improvements that have occurred over the last decade with chemotherapy. In patients with small-volume, resectable metastatic disease and T3-4 rectal (or obstructive) primary tumors, preoperative combined-modality therapy (5-fluorouracil/radiation therapy [5-FU/RT]) may be an acceptable option. In these cases, resection of both the rectal primary tumor and metastases is often performed after the combined-modality therapy and before systemic postoperative chemotherapy. Although there are limited data to support this regimen in patients with metastatic CRC, one could extrapolate the improved local control and decreased toxicity with preoperative versus postoperative chemoradiation reported by one group of researchers. Patients who have undergone complete resection of both the primary rectal cancer and all known metastatic disease can reasonably be considered to be candidates for standard postoperative management consistent with that given to patients with stage II or III rectal cancer.

Management of the Primary in Patients with Unresectable Metastatic Disease

The primary management of unresectable metastatic disease is systemic chemotherapy. Given the high response rates and low rates of overt rapid progression through current first-line regimens, this approach should be strongly considered in all cases except for those patients who are overtly obstructed or are extremely close to obstruction. As with all scenarios, however, care plans must be individualized to the particular needs of the patient, based on the pattern and pace of metastatic disease, degree of symptoms, risk of immanent obstruction, and comorbidities. Patients who have metastatic disease with small-volume unresectable metastases may be considered for palliative combined-modality

management of the pelvic disease. Since preoperative chemoradiotherapy followed by resection is the most effective modality for control of the rectal primary, patients who are judged to be at reasonable risk for survival long enough to develop symptoms from progressive or recurrent pelvic disease may be appropriately palliated with combined-modality therapy. Alternatively, systemic combination chemotherapy may be used first, with consideration of consolidative radiation and concurrent chemotherapy for more definitive local control in those patients who respond to therapy. In patients with bulky metastatic cancer, demise from metastatic cancer is more likely to occur before pelvic symptoms become a problem. In such patients, systemic chemotherapy is usually most appropriate, with local therapy best reserved following systemic chemotherapy for treating symptomatic complications as needed.

Cytotoxic and Targeted Therapies

5-fluorouracil (5-FU) has been the basis of standard chemotherapy for treating CRC for the last five decades. Overall, prolonged infusion schedules appear to be more effective and less toxic, and bolus regimens should rarely be used at this time. Capecitabine, an oral fluoropyrimidine, has been shown to have superior response rates and lower incidence of adverse events, but no significant differences in survival when compared to the Mayo Clinic schedule of bolus 5-FU/leucovorin (LV). This oral agent has a dose-limiting toxicity causing hand-foot syndrome, which appears to be more common in the U.S. population than in Europe, where most of the studies were done. In addition, capecitabine requires a highly motivated and reliable patient who will take oral medication correctly, will not miss or duplicate doses, and will hold medications at appropriate levels of toxicity.

Combining 5-FU/LV or capecitabine with newer agents, including irinotecan and oxaliplatin, has resulted in improved outcomes. Irinotecan, a topoisomerase I inhibitor, can be used independently in 5-FU-resistant advanced CRC, or can be combined with 5-FU/LV as first-line therapy in patients with metastatic disease. Oxaliplatin is a third-generation platinum compound and has emerged as a superior regimen to bolus 5-FU-irinotecan regimens. When faced with treating a patient with advanced CRC in the first-line setting, there are multiple options, and comparative trials have indicated that both FOLFOX (oxaliplatin-based) and FOLFIRI (irinotecan-based) are acceptable first-line regimens.

New "targeted" therapies such as cetuximab (Erbitux™), panitumumab (Vectibix™), and bevacizumab (Avastin™) have increased the options available for treating metastatic disease. Cetuximab and panitumumab are monoclonal antibodies directed against the epidermal growth factor receptor (EGFR). Cetuximab received U.S. Food and Drug Administration (FDA) approval for treatment of irinotecan-resistant disease. A 22% response rate was seen in patients treated with cetuximab/irinotecan, and an 11% response rate with cetuximab as a single agent. Panitumumab was recently FDA-approved after demonstrating improved progression-free survival versus best supportive care in patients with chemotherapy-refractory disease. Bevacizumab is directed against the vascular endothelial growth factor (VEGF). In a randomized phase III trial, adding bevacizumab 5mg/kg to IFL (leucovorin, fluorouracil, and irinotecan) in patients with advanced CRC improved overall survival by 4.5 months. However, in a larger phase III trial of oxaliplatin-based front-line chemotherapy, the addition

of bevacizumab resulted in a modest but significant improvement in progression-free survival, but no improvement in response rate and no significant impact on survival.

Bevacizumab has a half-life of 20 days. The safe interval between administration of bevacizumab and an operation has not been determined. The common practice of waiting 6 to 8 weeks (2-3 half-lives) between bevacizumab and an elective operation is consistent with an approval study in which the longest interval between bevacizumab and wound dehiscence was 56 days. A large study including unplanned operations had a mean of 20 days between bevacizumab and any wound-healing complication. A small study of planned hepatectomy after bevacizumab, with a mean interval of 6.9 weeks, found no increase in wound-healing complications when compared with matched controls. Delaying a planned operation 6 to 8 weeks after bevacizumab is today's reasonable consensus practice.

Supportive Care

Patients with widespread unresectable metastatic rectal cancer, poor performance status, and multiple comorbidities are often best managed with supportive, comfort-oriented intent.

Abbreviations

- 5-FU, 5-fluorouracil
- FOLFOX, oxaliplatin, 5-fluorouracil, and folinic acid
- FOLFIRI, leucovorin, 5-fluorouracil, and irinotecan
- KPS, Karnofsky performance status
- RFA, radiofrequency ablation
- RT, radiation therapy

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate procedures for treatment and management of patients with newly diagnosed metastatic rectal cancer

POTENTIAL HARMS

- Neoadjuvant chemotherapy is associated with potential adverse effects such as steatohepatitis and vascular changes, which may increase surgical complications.
- Capecitabine has a dose-limiting toxicity causing hand-foot syndrome, which appears to be more common in the U.S. population than in Europe, where most of the studies were done. In addition, capecitabine requires a highly motivated and reliable patient who will take oral medication correctly, will not miss or duplicate doses, and will hold medications at appropriate levels of toxicity.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Herman J, Messersmith WA, Johnstone PA, Blackstock AW, Konski AA, Mohiuddin M, Poggi MM, Regine WF, Rich TA, Suh WW, Cosman BC, Saltz L, Expert Panel on Radiation Oncology--Rectal/Anal Cancer. ACR Appropriateness Criteria® rectal cancer--metastatic disease at presentation. [online publication]. Reston (VA): American College of Radiology (ACR); 2007. 6 p. [27 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

SOURCE(S) OF FUNDING

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Rectal/Anal Cancer

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Joseph Herman, MD, MSc; Wells A. Messersmith, MD; Peter A. Johnstone, MD; A. William Blackstock, MD; Andre A. Konski, MD; Mohammed Mohiuddin, MD; Matthew M. Poggi, MD; William F. Regine, MD; Tyvin A. Rich, MD; W. Warren Suh, MD; Bard C. Cosman, MD; Leonard Saltz, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® *Anytime*, *Anywhere*™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.
- ACR Appropriateness Criteria® radiation dose assessment introduction. American College of Radiology. 2 p. Electronic copies: Available from the ACR Web site.

PATIENT RESOURCES

None available

NGC STATUS

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